

U.S. Patent Application No. 10/591,108
Supplemental Preliminary Amendment

RECEIVED
CENTRAL FAX CENTER

JAN 05 2007

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Original) A compound of the formula (I)



or a pharmaceutically acceptable salt thereof, wherein

Z is selected from the group consisting of phenyl; naphthyl; indenyl; C₃₋₇ cycloalkyl; indanyl; tetralinyl; decalinyl; heterocycle; and heterobicycle, wherein Z is optionally substituted with one or more R⁸, wherein R⁸ is independently selected from the group consisting of halogen; CN; OH; NH₂; oxo (=O), where the ring is at least partially saturated; R⁹; and R¹⁰;

R⁹ is selected from the group consisting of C₁₋₆ alkyl; O-C₁₋₆ alkyl; and S-C₁₋₆ alkyl, wherein R⁹ is optionally interrupted by oxygen and wherein R⁹ is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R¹⁰ is selected from the group consisting of phenyl; heterocycle; and C₃₋₇ cycloalkyl, wherein R¹⁰ is optionally substituted with one or more R¹¹, wherein R¹¹ is independently selected from the group consisting of halogen; CN; OH; NH₂; oxo (=O), where the ring is at least partially saturated; C₁₋₆ alkyl; O-C₁₋₆ alkyl; and S-C₁₋₆ alkyl;

R¹, R⁴ are independently selected from the group consisting of H; F; OH; and R^{4a};

R², R⁵ are independently selected from the group consisting of H; F; and R^{4b};

U.S. Patent Application No. 10/591,108
Supplemental Preliminary Amendment

R^{4a} is independently selected from the group consisting of C₁₋₆ alkyl; and O-C₁₋₆ alkyl, wherein R^{4a} is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{4b} is C₁₋₆ alkyl, wherein R^{4b} is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R³ is selected from the group consisting of H; and C₁₋₆ alkyl;

Optionally one or more pairs of R¹, R², R³, R⁴, R⁵ independently selected from the group consisting of R¹/R²; R²/R³; R³/R⁴; and R⁴/R⁵ form a C₃₋₇ cycloalkyl ring, which is optionally substituted with one or more of R¹², wherein R¹² is independently selected from the group consisting of F; Cl; and OH;

X is selected from the group consisting of S(O); S(O)₂; C(O); and C(R¹³R¹⁴);

R¹³, R¹⁴ are independently selected from the group consisting of H; F; C₁₋₆ alkyl; R¹⁵; and R¹⁶;

Optionally one or both pairs of R⁵, R¹³, R¹⁴ selected from the group consisting of R⁵/R¹³; and R¹³/R¹⁴ form a C₃₋₇ cycloalkyl ring, which is optionally substituted with one or more R¹⁷, wherein R¹⁷ is independently selected from the group consisting of F; Cl; and OH;

R¹⁵ is selected from the group consisting of phenyl; naphthyl; and indenyl, wherein R¹⁵ is optionally substituted with one or more R¹⁸, wherein R¹⁸ is independently selected from the group consisting of R¹⁹; R²⁰; halogen; CN; COOH; OH; C(O)NH₂; S(O)₂NH₂; S(O)NH₂; C₁₋₆ alkyl; O-C₁₋₆ alkyl; S-C₁₋₆ alkyl; COO-C₁₋₆ alkyl; OC(O)-C₁₋₆ alkyl; C(O)N(R²¹)-C₁₋₆ alkyl; S(O)₂N(R²¹)-C₁₋₆ alkyl; S(O)N(R²¹)-C₁₋₆ alkyl; S(O)₂-C₁₋₆ alkyl; S(O)-C₁₋₆ alkyl; N(R²¹)S(O)₂-C₁₋₆ alkyl; and N(R²¹)S(O)-C₁₋₆ alkyl, wherein each C₁₋₆ alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

U.S. Patent Application No. 10/591,108
Supplemental Preliminary Amendment

R^{16} is selected from the group consisting of heterocycle; heterobicycle; C_{3-7} cycloalkyl; indanyl; tertralinyl; and decaliny, wherein R^{16} is optionally substituted with one or more R^{22} , wherein R^{22} is independently selected from the group consisting of R^{18} ; R^{20} ; halogen; CN; OH; oxo (=O), where the ring is at least partially saturated; NH_2 ; COOH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; C_{1-6} alkyl; O- C_{1-6} alkyl; S- C_{1-6} alkyl; $N(R^{23})-C_{1-6}$ alkyl; COO- C_{1-6} alkyl; OC(O)- C_{1-6} alkyl; $C(O)N(R^{23})-C_{1-6}$ alkyl; $N(R^{23})-C(O)-C_{1-6}$ alkyl; $S(O)_2N(R^{23})-C_{1-6}$ alkyl; $S(O)N(R^{23})-C_{1-6}$ alkyl; $S(O)_2-C_{1-6}$ alkyl; $S(O)-C_{1-6}$ alkyl; $N(R^{23})S(O)_2-C_{1-6}$ alkyl; and $N(R^{23})S(O)-C_{1-6}$ alkyl, wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{19} is selected from the group consisting of phenyl; and naphthyl, wherein R^{19} is optionally substituted with one or more R^{24} , wherein R^{24} is independently selected from the group consisting of halogen; CN; COOH; OH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; C_{1-6} alkyl; O- C_{1-6} alkyl; S- C_{1-6} alkyl; COO- C_{1-6} alkyl; OC(O)- C_{1-6} alkyl; $C(O)N(R^{25})-C_{1-6}$ alkyl; $S(O)_2N(R^{25})-C_{1-6}$ alkyl; $S(O)N(R^{25})-C_{1-6}$ alkyl; $S(O)_2-C_{1-6}$ alkyl; $S(O)-C_{1-6}$ alkyl; $N(R^{25})S(O)_2-C_{1-6}$ alkyl; and $N(R^{25})S(O)-C_{1-6}$ alkyl, wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{20} is selected from the group consisting of heterocycle; heterobicycle; and C_{3-7} cycloalkyl; wherein R^{20} is optionally substituted with one or more R^{26} , wherein R^{26} is independently selected from the group consisting of halogen; CN; OH; oxo (=O), where the ring is at least partially saturated; NH_2 ; COOH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; C_{1-6} alkyl; O- C_{1-6} alkyl; S- C_{1-6} alkyl; $N(R^{27})-C_{1-6}$ alkyl; COO- C_{1-6} alkyl; OC(O)- C_{1-6} alkyl; $C(O)N(R^{27})-C_{1-6}$ alkyl; $N(R^{27})-C(O)-C_{1-6}$ alkyl; $S(O)_2N(R^{27})-C_{1-6}$ alkyl; $S(O)N(R^{27})-C_{1-6}$ alkyl; $S(O)_2-C_{1-6}$ alkyl; $S(O)-C_{1-6}$ alkyl; $N(R^{27})S(O)_2-C_{1-6}$ alkyl; and $N(R^{27})S(O)-C_{1-6}$ alkyl wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

U.S. Patent Application No. 10/591,108
Supplemental Preliminary Amendment

R^{21} , R^{23} , R^{25} , R^{27} are independently selected from the group consisting of H; and C_{1-6} alkyl, which is optionally substituted with one or more of R^{28} , wherein R^{28} is independently selected from the group consisting of F; Cl and OH;

R^6 , R^7 are independently selected from the group consisting of H; $(C(R^{29}R^{30}))_m-X^1-Z^1$; $(C(R^{31}R^{32}))_n-X^2-X^3-Z^2$; and C_{1-4} alkyl, which is substituted with one or more R^{29a} , wherein R^{29a} is independently selected from the group consisting of R^{29b} ; and Z^1 , provided that R^6 , R^7 are selected so that not both of R^6 , R^7 are independently selected from the group consisting of H; CH_3 ; CH_2CH_3 ; $CH_2CH_2CH_3$; and $CH(CH_3)_2$;

R^{29} , R^{29b} , R^{30} , R^{31} , R^{32} are independently selected from the group consisting of H; halogen; CN; OH; NH_2 ; $COOH$; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; C_{1-6} alkyl; $O-C_{1-6}$ alkyl; $N(R^{32a})-C_{1-6}$ alkyl; $COO-C_{1-6}$ alkyl; $OC(O)-C_{1-6}$ alkyl; $C(O)N(R^{32a})-C_{1-6}$ alkyl; $N(R^{32a})-C(O)-C_{1-6}$ alkyl; $S(O)_2N(R^{32a})-C_{1-6}$ alkyl; $S(O)N(R^{32a})-C_{1-6}$ alkyl; $S(O)_2-C_{1-6}$ alkyl; $S(O)-C_{1-6}$ alkyl; $N(R^{32a})S(O)_2-C_{1-6}$ alkyl; and $N(R^{32a})S(O)-C_{1-6}$ alkyl wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{32a} is selected from the group consisting of H; and C_{1-6} alkyl, which is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

Optionally one or more pairs of R^{29} , R^{30} , R^{31} , R^{32} independently selected from the group consisting of R^{29}/R^{30} ; and R^{31}/R^{32} form a C_{3-7} cycloalkyl ring, which is optionally substituted with one or more R^{32b} , wherein R^{32b} is independently selected from the group consisting of F; Cl; and OH;

m is 0, 1, 2, 3 or 4;

n is 2, 3 or 4;

U.S. Patent Application No. 10/591,108
Supplemental Preliminary Amendment

X¹ is independently selected from the group consisting of a covalent bond; -C₁₋₆ alkyl-; -C₁₋₆ alkyl-O-; -C₁₋₆ alkyl-N(R³³)-; -C(O)-; -C(O)-C₁₋₆ alkyl-; -C(O)-C₁₋₆ alkyl-O-; -C(O)-C₁₋₆ alkyl-N(R³³)-; -C(O)O-; -C(O)O-C₁₋₆ alkyl-; -C(O)O-C₁₋₆ alkyl-O-; -C(O)O-C₁₋₆ alkyl-N(R³³)-; -C(O)N(R³³)-; -C(O)N(R³³)-C₁₋₆ alkyl-; -C(O)N(R³³)-C₁₋₆ alkyl-O-; -C(O)N(R³³)-C₁₋₆ alkyl-N(R³⁴)-; -S(O)₂-; -S(O)-; -S(O)₂-C₁₋₆ alkyl-; -S(O)-C₁₋₆ alkyl-; -S(O)₂-C₁₋₆ alkyl-O-; -S(O)-C₁₋₆ alkyl-O-; -S(O)₂-C₁₋₆ alkyl-N(R³³)-; and -S(O)-C₁₋₆ alkyl-N(R³³)-; wherein each C₁₋₆ alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

X² is selected from the group consisting of -O-; -S-; -S(O)-; S(O)₂-; and -N(R³⁵)-;

X³ is selected from the group consisting of a covalent bond; -C₁₋₆ alkyl-; -C₁₋₆ alkyl-O-; -C₁₋₆ alkyl-N(R³⁶)-; -C(O)-; -C(O)-C₁₋₆ alkyl-; -C(O)-C₁₋₆ alkyl-O-; -C(O)-C₁₋₆ alkyl-N(R³⁶)-; -C(O)O-; -C(O)O-C₁₋₆ alkyl-; -C(O)O-C₁₋₆ alkyl-O-; -C(O)O-C₁₋₆ alkyl-N(R³⁶)-; -C(O)N(R³⁶)-; -C(O)N(R³⁶)-C₁₋₆ alkyl-; -C(O)N(R³⁶)-C₁₋₆ alkyl-O-; and -C(O)N(R³⁶)-C₁₋₆ alkyl-N(R³⁷)-; wherein each C₁₋₆ alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

Optionally X²-X³ are independently selected from the group consisting of -N(R³⁵)-S(O)₂-; -N(R³⁵)-S(O)-; -N(R³⁵)-S(O)₂-C₁₋₆ alkyl-; -N(R³⁵)-S(O)-C₁₋₆ alkyl-; -N(R³⁵)-S(O)₂-C₁₋₆ alkyl-O-; -N(R³⁵)-S(O)-C₁₋₆ alkyl-O-; -N(R³⁵)-S(O)₂-C₁₋₆ alkyl-N(R³⁶)-; and -N(R³⁵)-S(O)-C₁₋₆ alkyl-N(R³⁶)-; wherein each C₁₋₆ alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R³³, R³⁴, R³⁵, R³⁶, R³⁷ are independently selected from the group consisting of H; and C₁₋₆ alkyl, which is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

Z¹, Z² are independently selected from the group consisting of Z³; and -C(R^{37a})Z^{3a}Z^{3b};

U.S. Patent Application No. 10/591,108
Supplemental Preliminary Amendment

R^{37a} is selected from the group consisting of H; and C_{1-6} alkyl, which is optionally substituted with one or more F;

Z^3 , Z^{3a} , Z^{3b} are independently selected from the group consisting of H; T^1 ; T^2 ; C_{1-6} alkyl; C_{1-6} alkyl- T^1 ; and C_{1-6} alkyl- T^2 ; wherein each C_{1-6} alkyl is optionally substituted with one or more R^{37b} , wherein R^{37b} is independently selected from the group consisting of halogen; CN; OH; NH_2 ; COOH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; C_{1-6} alkyl; O- C_{1-6} alkyl; $N(R^{37c})-C_{1-6}$ alkyl; COO- C_{1-6} alkyl; OC(O)- C_{1-6} alkyl; $C(O)N(R^{37c})-C_{1-6}$ alkyl; $N(R^{37c})-C(O)-C_{1-6}$ alkyl; $S(O)_2N(R^{37c})-C_{1-6}$ alkyl; $S(O)N(R^{37c})-C_{1-6}$ alkyl; $S(O)_2-C_{1-6}$ alkyl; $S(O)-C_{1-6}$ alkyl; $N(R^{37c})S(O)_2-C_{1-6}$ alkyl; and $N(R^{37c})S(O)-C_{1-6}$ alkyl; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

T^1 is selected from the group consisting of phenyl; naphthyl; and indenyl; wherein T^1 is optionally substituted with one or more R^{38} ; wherein R^{38} is independently selected from the group consisting of halogen; CN; R^{39} ; COOH; OH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; COOT³; OT³; ST³; $C(O)N(R^{40})T^3$; $S(O)_2N(R^{40})T^3$; $S(O)N(R^{40})T^3$ and T³;

T^2 is selected from the group consisting of C_{3-7} cycloalkyl; indanyl; tetralinyl; decalinyl; heterocycle; and heterobicycle; wherein T^2 is optionally substituted with one or more R^{41} , wherein R^{41} is independently selected from the group consisting of halogen; CN; R^{42} ; OH; oxo (=O), where the ring is at least partially saturated; NH_2 ; COOH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; COOT³; OT³; $C(O)N(R^{43})T^3$; $S(O)_2N(R^{43})T^3$; $S(O)N(R^{43})T^3$; $N(R^{43})T^3$; and T³;

R^{39} is selected from the group consisting of C_{1-6} alkyl; O- C_{1-6} alkyl; S- C_{1-6} alkyl; COO- C_{1-6} alkyl; OC(O)- C_{1-6} alkyl; $C(O)N(R^{44})-C_{1-6}$ alkyl; $S(O)_2N(R^{44})-C_{1-6}$ alkyl; $S(O)N(R^{44})-C_{1-6}$ alkyl; S(O)- C_{1-6} alkyl; $S(O)_2-C_{1-6}$ alkyl; $N(R^{44})S(O)_2-C_{1-6}$ alkyl; and $N(R^{44})S(O)-C_{1-6}$ alkyl; wherein each C_{1-6} alkyl is optionally substituted with one more R^{45} , wherein R^{45} is independently selected from the group consisting of F; COOR⁴⁶; $C(O)N(R^{46}R^{47})$; $S(O)_2N(R^{46}R^{47})$; OR⁴⁶; $N(R^{46}R^{47})$; T³; O-T³; and $N(R^{46})-T^3$;

U.S. Patent Application No. 10/591,108
 Supplemental Preliminary Amendment

R^{42} is selected from the group consisting of C_{1-6} alkyl; $O-C_{1-6}$ alkyl; $S-C_{1-6}$ alkyl; $N(R^{48})-C_{1-6}$ alkyl; $COO-C_{1-6}$ alkyl; $OC(O)-C_{1-6}$ alkyl; $C(O)N(R^{48})-C_{1-6}$ alkyl; $N(R^{48})-C(O)-C_{1-6}$ alkyl; $S(O)_2N(R^{48})-C_{1-6}$ alkyl; $S(O)N(R^{48})-C_{1-6}$ alkyl; $S(O)-C_{1-6}$ alkyl; $S(O)_2-C_{1-6}$ alkyl; $-N(R^{48})S(O)_2-C_{1-6}$ alkyl; and $-N(R^{48})S(O)-C_{1-6}$ alkyl; wherein each C_{1-6} alkyl is optionally substituted with one or more R^{45} , wherein R^{45} is independently selected from the group consisting of F; $COOR^{49}$; $C(O)N(R^{49}R^{50})$; $S(O)_2N(R^{49}R^{50})$; $S(O)N(R^{49}R^{50})$; OR^{49} ; $N(R^{49}R^{50})$; T^3 ; $O-T^3$; and $N(R^{49})-T^3$;

R^{40} , R^{43} , R^{44} , R^{46} , R^{47} , R^{48} , R^{49} , R^{50} are independently selected from the group consisting of H; and C_{1-6} alkyl;

T^3 is selected from the group consisting of T^4 ; and T^5 ;

T^4 is selected from the group consisting of phenyl; naphthyl; and indenyl; wherein T^4 is optionally substituted with one or more R^{51} , wherein R^{51} is independently selected from the group consisting of halogen; CN; $COOR^{52}$; OR^{52} ; $C(O)N(R^{52}R^{53})$; $S(O)_2N(R^{52}R^{53})$; C_{1-6} alkyl; $O-C_{1-6}$ alkyl; $S-C_{1-6}$ alkyl; $COO-C_{1-6}$ alkyl; $OC(O)-C_{1-6}$ alkyl; $C(O)N(R^{52})-C_{1-6}$ alkyl; $S(O)_2N(R^{52})-C_{1-6}$ alkyl; $S(O)N(R^{52})-C_{1-6}$ alkyl; $S(O)_2-C_{1-6}$ alkyl; $S(O)-C_{1-6}$ alkyl; $N(R^{52})S(O)_2-C_{1-6}$ alkyl; and $N(R^{52})S(O)-C_{1-6}$ alkyl; wherein each C_{1-6} alkyl is optionally substituted with one more halogen selected from the group consisting of F; and Cl;

T^5 is selected from the group consisting of heterocycle; heterobicycle; C_{3-7} cycloalkyl; indanyl; tetralinyl; and decalinyl; wherein T^5 is optionally substituted with one or more R^{54} , wherein R^{54} is independently selected from the group consisting of halogen; CN; OR^{55} ; oxo (=O), where the ring is at least partially saturated; $N(R^{55}R^{56})$; $COOR^{55}$; $C(O)N(R^{55}R^{56})$; $S(O)_2N(R^{55}R^{56})$; $S(O)N(R^{55}R^{56})$; C_{1-6} alkyl; $O-C_{1-6}$ alkyl; $S-C_{1-6}$ alkyl; $N(R^{55})-C_{1-6}$ alkyl; $COO-C_{1-6}$ alkyl; $OC(O)-C_{1-6}$ alkyl; $C(O)N(R^{55})-C_{1-6}$ alkyl; $N(R^{55})-C(O)-C_{1-6}$ alkyl; $S(O)_2N(R^{55})-C_{1-6}$ alkyl; $S(O)N(R^{55})-C_{1-6}$ alkyl; $S(O)_2-C_{1-6}$ alkyl; $S(O)-C_{1-6}$ alkyl; $N(R^{55})S(O)_2-C_{1-6}$ alkyl; and $N(R^{55})S(O)-C_{1-6}$ alkyl; wherein each C_{1-6} alkyl is

U.S. Patent Application No. 10/591,108
Supplemental Preliminary Amendment

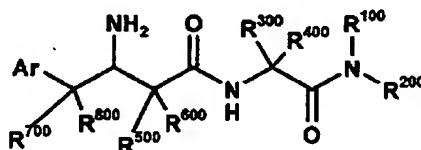
optionally substituted with one more halogen selected from the group consisting of F; and Cl;

R^{52} , R^{53} , R^{55} , R^{56} , are independently selected from the group consisting of H; and C_{1-6} alkyl;

with the proviso that the following compounds are excluded:

3-amino-N-cyclohexyl-4-phenyl-butyramide,
(S)-3-amino-N-[5-(6-dimethylamino-purin-9-yl)-4-hydroxy-2-hydroxymethyl-tetrahydrofuran-3-yl]-4-p-tolyl-butyramide,
(S)-2-((S)-2-amino-3-phenyl-propane-1-sulfonylamino)-3-phenyl-propionic acid,
(S)-3-amino-4,N-diphenyl-butyramide;

and with the further proviso that compounds according to the following formula are excluded:



wherein

Ar is phenyl optionally substituted with 1, 2, 3, 4, or 5 groups independently selected from halogen; C_{1-6} alkyl optionally substituted with 1 to 5 halogens; $O-C_{1-6}$ alkyl optionally substituted with 1 to 5 halogens; and cyano,

R^{500} , R^{600} , R^{700} , R^{800} are independently selected from H; and C_{1-6} alkyl, optionally substituted by 1 or 2 F,

U.S. Patent Application No. 10/591,108
Supplemental Preliminary Amendment

R^{300} and R^{400} are independently selected from hydrogen; C_{1-6} alkyl, which is optionally substituted by 1 or 2 F; and C_{3-7} cycloalkyl, optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from halogen and hydroxy,

R^{100} is selected from hydrogen; and C_{1-6} alkyl, optionally substituted by 1 or 2 F,

R^{200} is selected from hydrogen; C_{1-6} alkyl; C_{3-7} cycloalkyl; phenyl; HET1; C_{1-6} alkylphenyl; $-C_{1-6}$ alkylAR2; $-C_{1-6}$ alkyl- C_{3-7} cycloalkyl; $-C_{1-6}$ alkyl-HET1; $-C_{1-6}$ alkyl-HET2; $-C_{1-6}$ alkyl- CO_2C_{1-6} alkyl; $-C_{1-6}$ alkylOCO- C_{1-6} alkyl; $-C_{1-6}$ alkylCO- C_{1-6} alkyl; $-C_{1-6}$ alkylNHCO- C_{1-6} alkyl; $-C_{1-6}$ alkylCONH-alkyl; $-C_{1-6}$ alkylCON-di- C_{1-6} alkyl; $-C_{1-6}$ alkylNH- C_{1-6} alkyl; $-C_{1-6}$ alkylN-di- C_{1-6} alkyl; $-C_{1-6}$ alkylNHSO₂- C_{1-6} alkyl; $-C_{1-6}$ alkylSO₂NH- C_{1-6} alkyl; $-C_{1-6}$ alkylSO₂- C_{1-6} alkyl; and $-C_{1-6}$ alkylSO₂N-di(C_{1-6}) alkyl;

wherein each C_{1-6} alkyl is optionally substituted by 1 or 2 F; and

wherein phenyl, AR2, HET1, HET2 and C_{3-7} cycloalkyl are optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from phenyl (optionally substituted with halogen, trifluoromethyl, C_{1-4} alkyl or O- C_{1-4} alkyl), halogen, C_{1-6} alkyl, halo- C_{1-6} alkyl, dihalo- C_{1-6} alkyl, trifluoromethyl, O- C_{1-6} alkyl, carboxy- C_{1-6} alkyl, carboxy- C_{1-6} alkoxy, hydroxy, amino, C_{1-6} alkylamino, di- C_{1-6} alkylamino, $-CONH_2$, $-CONH-C_{1-6}$ alkyl, $CON-di(C_{1-6})alkyl$, $-NHCO-C_{1-6}$ alkyl, $-SO_2-C_{1-6}$ alkyl, SO_2NH_2 , $-SO_2NH-C_{1-6}$ alkyl, $SO_2N-diC_{1-6}alkyl$ and $-NHSO_2-C_{1-6}alkyl$,

further

R^{100} and R^{200} may together with the nitrogen to which they are attached form a ring defined by HET1 or HET3,

wherein a ring comprising R^{100} and R^{200} is optionally substituted by 1 or 2 substituents independently selected from halogen, C_{1-6} alkyl, O- C_{1-6} alkyl, cyano, carboxy, carboxy- C_{1-6} alkyl, $-CO_2-C_{1-6}$ alkyl, C_{1-6} alkylamino, di- (C_{1-6}) alkylamino, $-NHCO-C_{1-6}$ alkyl, $-CONH-C_{1-6}$ alkyl, $-CON-di-C_{1-6}$ alkyl and HET1, wherein each C_{1-6} alkyl group is optionally substituted by 1 or 2 substituents independently selected from hydroxy and fluoro;

U.S. Patent Application No. 10/591,108
Supplemental Preliminary Amendment

and

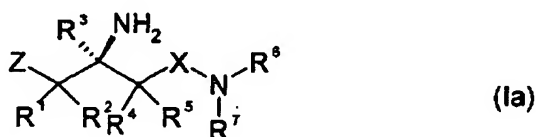
AR2 is a 8-, 9- or 10-membered unsaturated, partially or fully saturated bicyclic carbocyclic ring;

HET1 is a 3-, 4-, 5- or 6-membered, unsaturated, partially or fully saturated monocyclic heterocyclyl ring containing up to four heteroatoms independently selected from O, N, and S (but not containing any O-O, O-S or S-S bonds) linked via a ring carbon atom or a ring nitrogen atom if the ring is not thereby quaternised, and wherein an available carbon, sulfur or nitrogen atom may be oxidized;

HET2 is a 8-, 9- or 10-membered, unsaturated, partially or fully saturated bicyclic heterocyclyl ring containing up to four heteroatoms independently selected from O, N, and S (but not containing any O-O, O-S or S-S bonds) and linked via a ring carbon atom in either of the rings comprising the bicyclic system; and

HET3 is a N-linked saturated bicyclic ring system containing up to 12 ring atoms including the linking nitrogen atom.

2. (Original) A compound according to claim 1 of formula (Ia)



or a pharmaceutically acceptable salt thereof, wherein Z, R¹-R⁷ and X have the meaning as indicated in claim 1.

3. (Previously presented) A compound according to claim 1, wherein Z is phenyl or heterocycle.

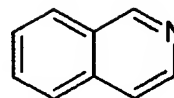
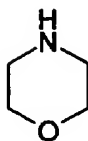
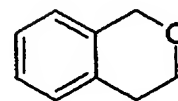
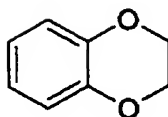
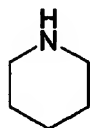
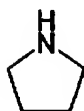
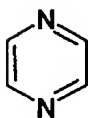
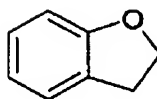
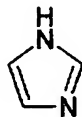
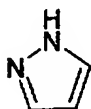
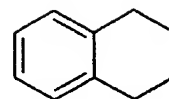
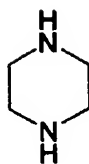
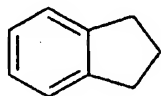
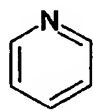
U.S. Patent Application No. 10/591,108
Supplemental Preliminary Amendment

4. (Previously presented) A compound according to claim 1, wherein Z is optionally substituted with 1 or 2 R⁸, which are the same or different.
5. (Previously presented) A compound according to claim 1, wherein R⁸ is selected from the group consisting of Cl; F; CN; CH₃; and OCH₃.
6. (Previously presented) A compound according to claim 1, wherein Z is 2-Fluorophenyl.
7. (Previously presented) A compound according to claim 1, wherein R¹, R⁴ are independently selected from the group consisting of H; F; OH; CH₃; and OCH₃.
8. (Previously presented) A compound according to claim 1, wherein R², R⁵ are independently selected from the group consisting of H; F; and CH₃.
9. (Previously presented) A compound according to claim 1, wherein R¹, R², R⁴, R⁵ are H.
10. (Previously presented) A compound according to claim 1, wherein R³ is H.
11. (Previously presented) A compound according to claim 1, wherein X is C(O) or S(O)₂.
12. (Previously presented) A compound according to claim 1, wherein R⁶ is selected from the group consisting of H; and CH₃.
13. (Previously presented) A compound according to claim 1, wherein X¹ is a covalent bond.

U.S. Patent Application No. 10/591,108
Supplemental Preliminary Amendment

14. (Previously presented) A compound according to claim 1, wherein m is 0, 1, 2 or 3.
15. (Previously presented) A compound according to claim 1, wherein R^7 is Z^1 .
16. (Previously presented) A compound according to claim 1, wherein R^7 is C_{1-4} alkyl, substituted with 1-4 R^{29a} , which are the same or different.
17. (Original) A compound according to claim 16, wherein R^7 is selected from the group consisting of $CH(R^{29a})_2$; $CHR^{29a}-CH_2R^{29a}$; $CH_2-CH(R^{29a})_2$; $CH_2-CHR^{29a}-CH_2R^{29a}$; and $CH_2-CH_2-CH(R^{29a})_2$.
18. (Previously presented) A compound according to claim 1, wherein R^{29a} is selected from the group consisting of R^{29b} ; and Z^1 ; and wherein R^{29b} is selected from the group consisting of H; F; Cl; NH_2 ; $NHCH_3$; $N(CH_3)_2$; CH_3 ; and C_2H_5 .
19. (Previously presented) A compound according to claim 1, wherein R^{29a} is selected from the group consisting of R^{29b} ; and Z^1 ; and wherein Z^1 is selected from the group consisting of T^1 ; and T^2 .
20. (Previously presented) A compound according to claim 1, wherein T^1 is phenyl; and wherein T^1 is optionally substituted with 1-3 R^{38} , which are the same or different.
21. (Previously presented) A compound according to claim 1, wherein R^{38} is independently selected from the group consisting of F; Cl; CN; CH_3 ; C_2H_5 ; $CH_2CH_2CH_3$; $CH(CH_3)_2$; CF_3 ; $O-CH_3$; $O-C_2H_5$; $S-CH_3$; SO_2NH_2 ; T^3 ; and $O-T^3$.
22. (Previously presented) A compound according to claim 1, wherein T^2 is selected from the group consisting of

U.S. Patent Application No. 10/591,108
Supplemental Preliminary Amendment



and wherein T^2 is optionally substituted with 1-2 R^{41} , which are the same or different.

23. (Previously presented) A compound according to claim 1, wherein R^{41} is selected from the group consisting of OH; CH_3 ; and T^3 ;

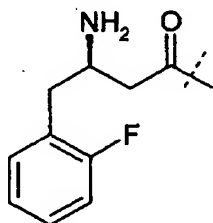
24. (Previously presented) A compound according to claim 1, wherein T^3 is T^4 .

25. (Previously presented) A compound according to claim 1, wherein T^4 is phenyl, wherein T^4 is optionally substituted with 1-3 R^{51} , which are the same or different.

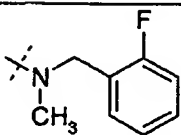
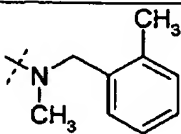
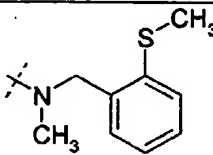
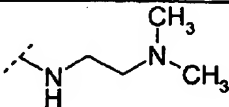
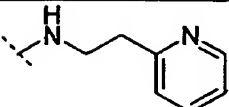
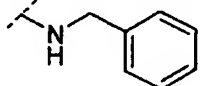
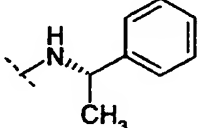
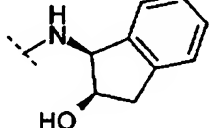
26. (Previously presented) A compound according to claim 1, wherein R^{51} is independently selected from the group consisting of F; Cl; CH_3 ; C_2H_5 ; $CH_2CH_2CH_3$; $CH(CH_3)_2$; CF_3 ; O- CH_3 ; O- C_2H_5 ; S- CH_3 ; and SO_2NH_2 .

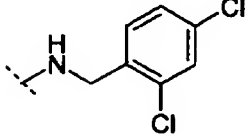
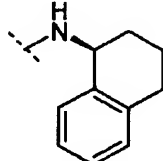
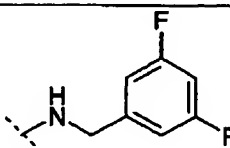
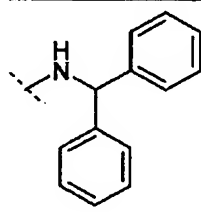
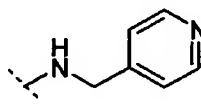
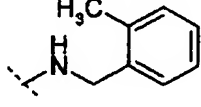
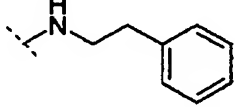
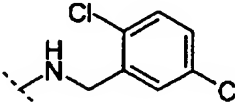
U.S. Patent Application No. 10/591,108
Supplemental Preliminary Amendment

27. (Previously presented) A compound according to claim 1, wherein T^3 is T^5 .
28. (Previously presented) A compound according to claim 1, wherein T^5 is heterocycle, wherein T^5 is optionally substituted with 1-2 R^{54} , which are the same or different.
29. (Previously presented) A compound according to claim 1, wherein R^{54} is selected from the group consisting of OH; and CH_3 .
30. (Original) A compound according to claim 1 selected from the group consisting of

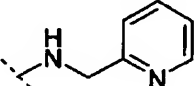
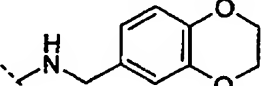
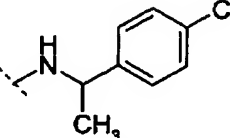
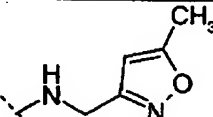
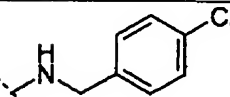
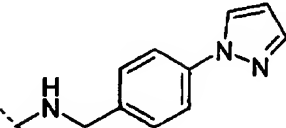
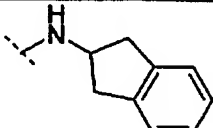
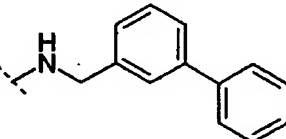
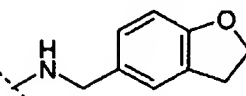
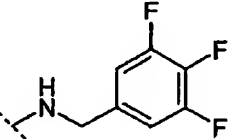
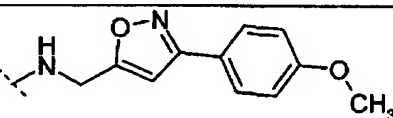
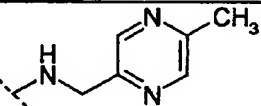
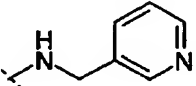
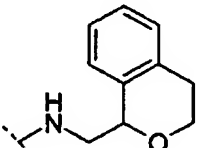
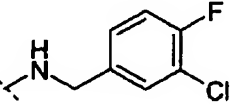
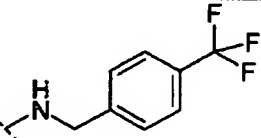
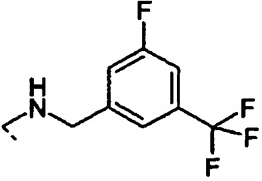


U.S. Patent Application No. 10/591,108
Supplemental Preliminary Amendment

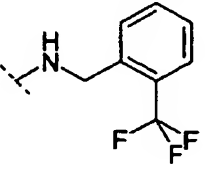
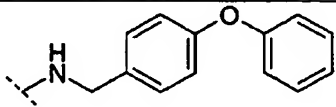
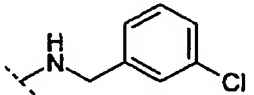
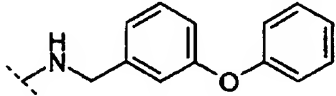
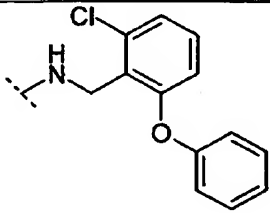
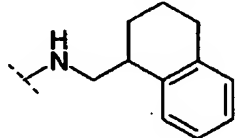
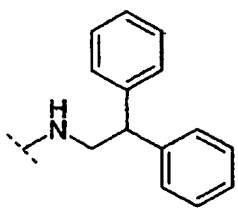
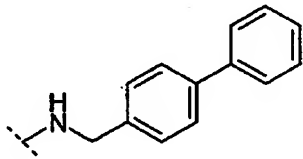
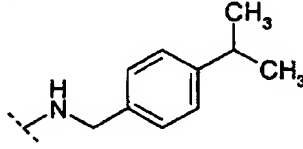
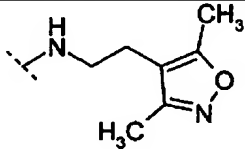
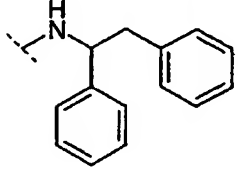
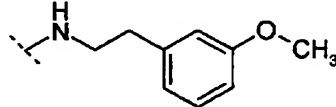
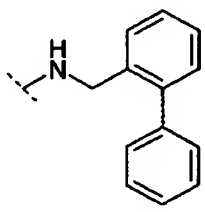
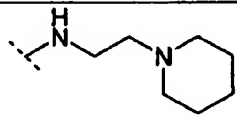
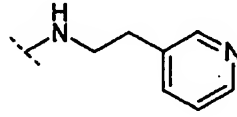
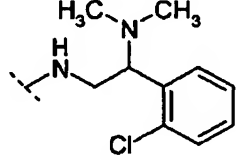
4	
5	
6	
7	
8	
9	
10	
11	

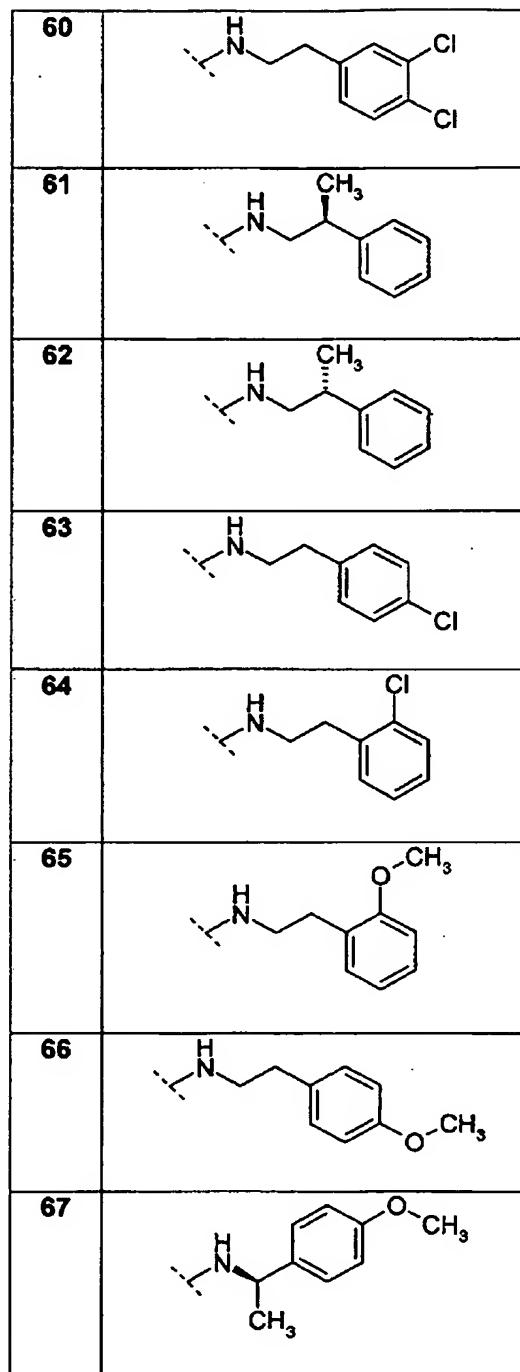
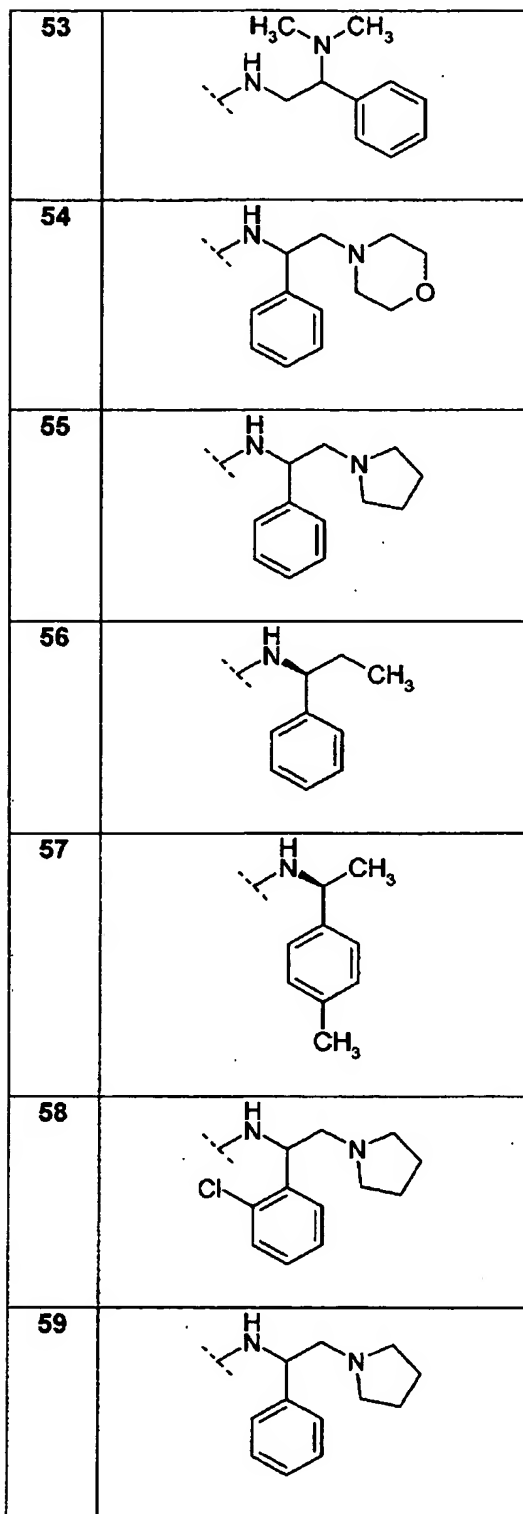
12	
13	
14	
15	
16	
17	
18	
19	

U.S. Patent Application No. 10/591,108
Supplemental Preliminary Amendment

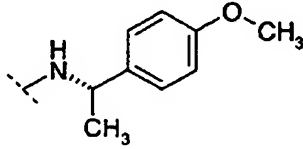
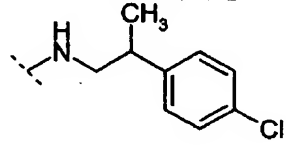
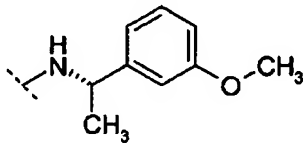
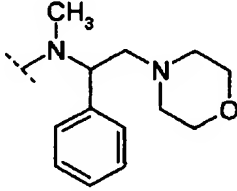
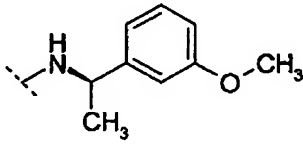
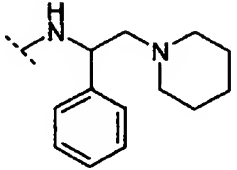
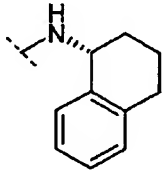
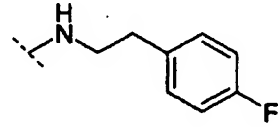
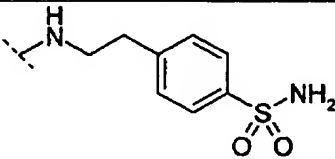
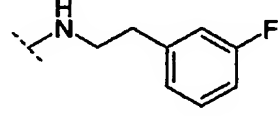
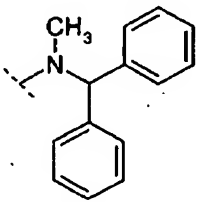
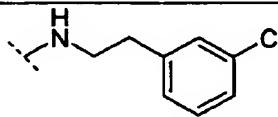
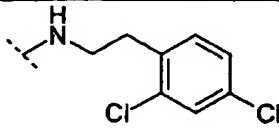
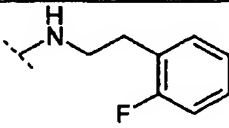
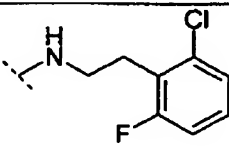
20		29	
21		30	
22		31	
23		32	
24		33	
25		34	
26		35	
27		36	
28			

U.S. Patent Application No. 10/591,108
Supplemental Preliminary Amendment

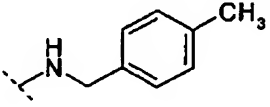
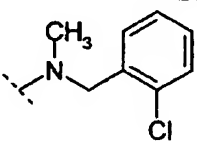
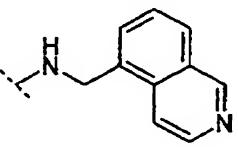
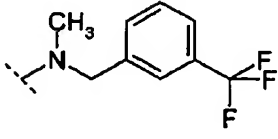
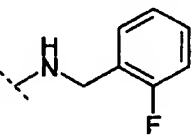
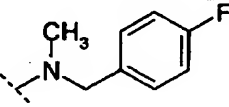
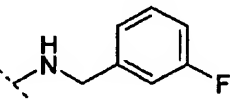
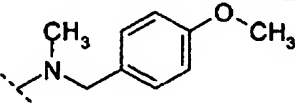
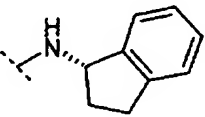
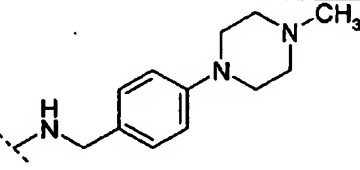
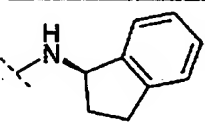
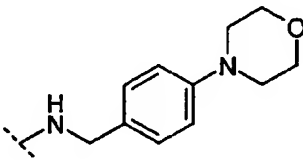
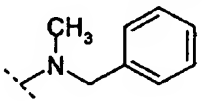
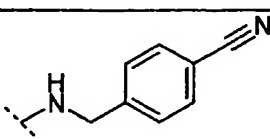
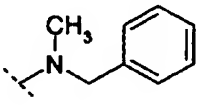
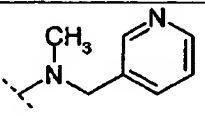
37		44	
38		45	
39		46	
40		47	
41		48	
42		49	
43		50	
		51	
		52	

U.S. Patent Application No. 10/591,108
Supplemental Preliminary Amendment

U.S. Patent Application No. 10/591,108
Supplemental Preliminary Amendment

68		75	
69		76	
70		77	
71		78	
72		79	
73		80	
74		81	
		82	

U.S. Patent Application No. 10/591,108
Supplemental Preliminary Amendment

83		92	
84		93	
85		94	
86		95	
87		96	
88		97	
89		98	
90			
91			

U.S. Patent Application No. 10/591,108
Supplemental Preliminary Amendment

31. (Previously presented) A prodrug compound of a compound according to claim 1.
32. (Currently amended) A pharmaceutical composition comprising said compound or said pharmaceutically acceptable salt thereof or a prodrug thereof according to claim 1 together with a pharmaceutically acceptable carrier.
33. (Currently amended) A pharmaceutical composition according to claim 32, comprising one or more additional compounds or pharmaceutically acceptable salts thereof selected from the group consisting of another of said compound or said pharmaceutically acceptable salt thereof or a prodrug thereof; another DPP-IV inhibitor; insulin sensitizers; PPAR agonists; biguanides; protein tyrosinephosphatase-1B (PTP-1B) inhibitors; insulin and insulin mimetics; sulfonylureas and other insulin secretagogues; α -glucosidase inhibitors; glucagon receptor antagonists; GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists; GIP, GIP mimetics, and GIP receptor agonists; PACAP, PACAP mimetics, and PACAP receptor 3 agonists; cholesterol lowering agents; HMG-CoA reductase inhibitors; sequestrants; nicotiny alcohol; nicotinic acid or a salt thereof; PPAR α agonists; PPAR γ dual agonists; inhibitors of cholesterol absorption; acyl CoA : cholesterol acyltransferase inhibitors; anti-oxidants; PPAR α agonists; antiobesity compounds; an ileal bile acid transporter inhibitor; and anti-inflammatory agents.
34. (Currently amended) A compound or a pharmaceutically acceptable salt thereof or a prodrug thereof of claim 1 for use as a medicament.
35. (Currently amended) A method for the treatment or prophylaxis of non-insulin dependent (Type II) diabetes mellitus; hyperglycemia; obesity; insulin resistance; lipid disorders; dyslipidemia; hyperlipidemia; hypertriglyceridemia; hypercholesterolemia; low HDL; high LDL; atherosclerosis; growth hormone deficiency; diseases related to the immune response; HIV infection; neutropenia; neuronal disorders; tumor metastasis; benign

U.S. Patent Application No. 10/591,108
Supplemental Preliminary Amendment

prostatic hypertrophy; gingivitis; hypertension; osteoporosis; diseases related to sperm motility; low glucose tolerance; insulin resistance; its sequelae; vascular restenosis; irritable bowel syndrome; inflammatory bowel disease; including Crohn's disease and ulcerative colitis; other inflammatory conditions; pancreatitis; abdominal obesity; neurodegenerative disease; anxiety; depression; retinopathy; nephropathy; neuropathy; Syndrome X; ovarian hyperandrogenism (polycystic ovarian syndrome; Type 2 diabetes; or growth hormone deficiency, comprising administering to a subject in need of said treatment said compound or said pharmaceutically acceptable salt thereof or a prodrug thereof of claim 1.

36. (Currently amended) A method to inhibit DPP-IV peptidase activity comprising administering said compound or said pharmaceutically acceptable salt thereof or a prodrug thereof of claim 1 to a subject in an amount sufficient to inhibit DPP-IV peptidase activity.